Intravenous Alpha Lipoic Acid in Cancer Care

Healthcare Provider Resource

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Developed by:
The Patterson Institute for Integrative Oncology Research
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Table of Contents

General information

Common name:
Alpha-lipoic Acid (ALA)

Alternate names:
Thioctic Acid; Lipoic Acid; Acetate Replacing Factor; R-ALA; S-ALA; Thioctacid, 1,2-Dithiolane-3-pentanoic acid, 6,8-dithiooctanoic acid.

Routes of administration:
Intravenous (IV), oral, vaginal suppository (only IV will be reviewed in this monograph).

Reported uses in cancer care:
IV ALA has been used by integrative cancer care practitioners with goals of improving survival, tumor response and quality of life (QoL), and alleviating chemotherapy side effects such as peripheral neuropathy.

Summary

IV ALA is mainly used in integrative cancer care for its antioxidant properties, as a means to stimulate glutathione synthesis, strengthen the effects of other antioxidants (e.g., vitamin C and E), and enhance insulin signaling. In total, seven studies reporting on 46 patients were included in this review: two single-arm studies, two case series, and three case reports. Almost all studies involved patients with advanced or metastatic cancer. IV doses ranged from 300-600 mg, with the most common frequency being once per week. Reported outcomes include managing symptoms and side effects, QoL, tumor response, and survival. Preliminary research from two small single-arm trials in patients receiving platinum-based agents alongside IV ALA reported that half the participants experienced a reduction in the severity of chemotherapy-induced peripheral neuropathy. There is insufficient data to comment on other clinical outcomes. There are some preclinical reports of ALA having possible anticancer properties. Safety data is limited in people with cancer; however, systematic reviews report that IV ALA is considered safe and tolerable in patients with diabetic neuropathy. Overall, there is insufficient evidence to comment on the efficacy or interaction potential of IV ALA in the context of cancer management. More clinical research is needed.

Background

ALA is an organosulfur compound produced by the human body in small amounts.[1] ALA has many properties; in mitochondria, it is used as a cofactor for enzymatic complexes,[2] including energy production through the Kreb's cycle.[1] It is used in various conditions due to its antioxidant properties, cardiovascular and cognitive effects, anti-aging, detoxifying, anti-inflammatory, anti-cancer, and neuroprotective properties.[3]

Clinical trials using ALA, mainly orally, have suggested benefits for weight loss,[4-6] ameliorating diabetic neuropathy,[7-9] reducing side effects of antipsychotic medications,[10-12] improving symptoms of multiple sclerosis,[13,14] reducing miscarriage risk,[15-17] and reducing inflammation and oxidative stress in patients after organ transplantation.[18,19]

Interest in ALA in cancer care has stemmed from its potential anticancer effects *in vitro* and its ability to improve neuropathy. This monograph summarizes the available literature on the use of ALA in cancer.

Methods

Monographs are created by the Patterson Institute for Integrative Oncology Research team and are updated approximately every two years, or when significant new literature is published. An update on a previous search was completed in Medline and Cochrane Library for IV ALA on January 20, 2023. The previous search was from database inception. Eligibility criteria included English-language human studies in cancer reporting on efficacy, QoL, safety, or feasibility. A scoping review was performed to identify missing papers and background information. The papers were screened by two reviewers independently. Data was summarized into healthcare provider and patient monographs.

Pharmacokinetics

ALA is synthesized in humans in small amounts and it is mainly obtained from dietary sources such as organ meat, red meat, vegetables (spinach, tomatoes, broccoli), and fruits.[1,20,21] ALA is reduced to dihydrolipoic acid (DHLA) and eventually re-oxidized in the formation of nicotinamide adenine dinucleotide hydride (NADH). In this way, ALA and DHLA act as a redox couple transferring electrons to and from other substances.[20,21]

ALA naturally exists in two enantiomeric forms, the R-enantiomer is the naturally occurring form,[22] and shows increased bioavailability and better pharmacokinetic parameters (rapid absorption and high plasma concentration) as compared to its S-enantiomer.[1,23,24] When the racemic form is used, typically both enantiomers are present in equal proportions.

The pharmacokinetics of intravenously and orally administered ALA vary slightly. ALA is quickly metabolized in the liver and excreted by the kidneys and therefore has limited bioavailability and short half life after oral administration.[23,25] Furthermore, ALA is highly sensitive to heat and light and has reduced bioavailability in its oral form if taken with food.[26,27] However the use of innovative techniques like amphiphilic matrices improves its bioavailability and increases its solubility.[1] When ingested in doses ranging from 50-600 mg, ALA is detectable for up to 4 hours in serum and reaches a maximal blood concentration 0.5 to 1 hour after ingestion.[1,28] The maximum plasma concentration of the R-enantiomer was found to be 40-50% percent higher than the S enantiomer.[23] When administered by IV, ALA is detectable for up to 2 hours after administration achieving a greater mean peak plasma levels (Cmax) compared to the oral route.[1,28]

Mechanism of Action

The therapeutic activity of ALA is mainly attributed to its antioxidant properties. As an antioxidant, ALA's functions include metal chelation, scavenging reactive oxygen species (ROS), regenerating endogenous antioxidants, and repairing oxidative damage.[20,21] Data on its impact on glucose metabolism, and preliminary data investigating the anticancer effects of ALA are also emerging.[21,29,30]

Antioxidant properties

ALA is a direct ROS scavenger in both its oxidized and reduced forms (DHLA).[20,21] As ROS scavengers, ALA and DHLA chelate redox-active metals including free iron, copper, manganese and zinc, which prevents them from inducing oxidative damage.[20,21] ALA is also a potent redox-regulator (meaning it prevents oxidative stress) of proteins such as myoglobin, methionine, prolactin, thioredoxin and NF-kB transcription factor.[20,22] In addition, DHLA as a potent reducing agent has the ability to reduce and regenerate many crucial antioxidants including vitamin C, vitamin E and

glutathione.[20,21] This antioxidant capacity has been demonstrated clinically in one study of patients with advanced cancer.[31]

Glucose and insulin metabolism

Most studies and systematic reviews looked at the impact of ALA on glucose find a significant reduction in blood glucose and insulin, although some studies have found minimal impact.[32-35] Hyperglycemia, commonly seen in diabetes and cancer, potentiates oxidative stress that can lead to neuronal and endothelial damage.[21] It is speculated that ALA plays a role in the treatment and prevention of chemotherapy-induced peripheral neuropathy (CIPN) by participating in insulin production and enhancing glucose uptake in insulin-sensitive and insulin-resistant muscle tissue.[21]

Anticancer effects

In addition to these primary mechanisms of action, several others have been proposed which relate to its possible role in cancer management.

One idea surrounds ALA's ability to induce hyperacetylation of histones.[30] By inhibiting histones, ALA may be able to drive cancerous cells towards apoptosis. ALA has also been shown to inhibit the protein complex NF-kB (nuclear factor kB). If activated, NF-kB can increase the survival of cancerous cells and increase cellular transformation, metastasis, invasion, proliferation, chemo-resistance, radio-resistance, and inflammation.[21,30] ALA exhibits antimutagenic and anticlastogenic properties, classifying it as part of the group of natural antimutagens.[21]

Cancer cells rely on aerobic glycolysis for their energy by converting glucose to lactate for ATP generation, a phenomenon known as the Warburg effect.[1] Through activation of pyruvate dehydrogenase (PDH), ALA can inhibit aerobic glycolysis and lactate production, which may produce an anticancer effect.[36,37] By increasing the uptake of oxidizable substrates into the mitochondrion of cancerous cells, ALA is also able to stimulate pro-oxidant driven apoptosis.[30] Finally, ALA is being investigated for its ability to correct functional defects in peripheral blood mononuclear cells in advanced cancer patients.[29]

Clinical Evidence Related to Effectiveness

There are seven studies on the use of IV ALA in humans with cancer, these include two single-arm trials,[38,39] two case series,[30,40] and three case reports.[41-43] Although there are numerous preclinical studies looking at the use of ALA alone or in combination with other agents, clinical data is limited. There is insufficient evidence to determine the efficacy or safety of IV ALA in the context of integrative cancer support.

ALA in combination with low-dose naltrexone (LDN)

There are two case reports and two case series documenting improved symptoms and longer than expected survival following treatment with ALA and low-dose naltrexone (LDN). Of note, all but one[40] was published by the same authors.

One case report describes treatment of a 46-year-old male with poorly differentiated adenocarcinoma of the pancreas with metastases to the liver, who had previously failed chemotherapy and continued to have disease progression on standard treatment.[42] This patient had immediate improvement in symptoms after starting the IV ALA+LDN protocol, and 78 months after beginning this treatment was free from symptoms with no disease progression. In another publication in pancreatic cancer, case studies are presented of three patients, all with poor prognosis, who were treated with an IV

ALA+LDN protocol.[30] One person was still alive and free of any signs and symptoms 39 months after initial diagnosis (at the time of publication) without any standard therapies. A second person was treated for six months and observed an increased QoL, improvement of all symptoms, and no signs of disease recurrence on a PET scan. A third person exhibited immediate improvement in symptoms and was well enough to undergo surgery.

An additional case report describes a 61 year old man with follicular lymphoma who was first treated with a series of nine IV ALA therapies followed by six months of LDN.[41] After 6 months of therapy the patient had complete resolution of multiple large, metabolically active, pathologic lymph nodes, and remained symptom free at the time of publication (1-year).

Finally, a case series included 11 patients with advanced metastatic cancer, 10 of whom were considered chemoresistant and offered palliative care only.[40] They received what the authors described as a metabolic treatment of 600 mg/day IV lipoic acid, 500 mg 3x/day of hydroxycitrate (HCA), and 5 mg of LDN at bedtime. Two patients died due to cancer progression within two months. Another two patients were switched to chemotherapy combined with metabolic treatment, and of those, one reported a dramatic tumor response. The rest of the patients had either stable or slow disease progression. None of the patients experienced significant side effects. Case 11 in this series had advanced hormone-resistant prostate cancer and received anti-androgen therapy in addition to 600 mg IV lipoic acid and 500 mg of HCA/day and experienced a 90% decrease in PSA levels. Authors suggest these preliminary results imply a lack of toxicity and possible efficacy of metabolic treatment in advanced chemoresistant carcinoma.

ALA in combination with other natural health products (NHPs)

A case report described a 64-year-old man with stage 4 renal cell carcinoma (RCC) with lung metastases who progressed on conventional treatment and then received a multimodal treatment including IV ALA.[43] The treatment consisted of IV racemic ALA, IV vitamin C, oral LDN, oral NHPs (ALA, selenomethionine silymarin, and a B complex), a strict diet, exercise, and a stress-reduction program. The patient's general condition improved a few weeks after starting treatment, with complete resolution of the left lung mass. The patient had no evidence of disease after 9-years of follow-up. No side effects were reported.

ALA for chemotherapy-induced peripheral neuropathy (CIPN)

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect associated with neurotoxic chemotherapeutics, most commonly platinum and taxane agents. Two single-arm trials published by the same authors found an improvement in neuropathy symptoms.[38,39] In an open, uncontrolled trial aimed at investigating the therapeutic potential of IV ALA to ameliorate oxaliplatin induced peripheral neuropathy, 15 patients with colorectal cancer with ≥ grade 2 oxaliplatin induced peripheral sensory neuropathy were treated with a combination of IV ALA (600 mg once a week for 3-5 weeks) followed by oral ALA (600 mg three times daily for a maximum of 6 months).[38] Eight of the fifteen patients (53%) demonstrated a reduction in the severity of neurologic symptoms, improving by at least one grade. The seven patients who did not demonstrate a significant improvement all had advanced stages of peripheral neuropathy. A separate uncontrolled study by the same authors administered 600 mg ALA by IV once weekly for 3-5 weeks followed by oral supplementation to patients experiencing grade 2-3 polyneuropathy during or after docetaxel-cisplatin chemotherapy treatment.[39]

Fourteen patients were enrolled, of whom eight (57%) experienced an improvement in neurological symptoms. The median time to improvement was 4 weeks. Adverse events included moderate gastric pain and mild nausea in two patients each. Larger, randomized controlled trials are needed to replicate these findings.

Although studies on the use of IV ALA for CIPN are limited, systematic reviews (SRs) and meta-analyses have been published supporting the safe and effective use of IV ALA in diabetic neuropathy.[44-46] One analysis of over 1,250 patients with diabetic neuropathy who were treated with 600 mg/day of IV ALA concluded that as little as three weeks of treatment reduced symptoms.[45] Another SR on four RCTs found that IV administration resulted in a clinically significant improvement in neuropathic pain.[46] Researchers suggested that ALA might have greater efficacy when administered intravenously, compared to orally. ALA has also been shown to improve both somatic and autonomic neuropathies by regulating endoneural blood flow, improving vascular dysfunction, and reducing oxidative stress.[38]

Oral ALA use

Although intravenous administration of ALA is the focus of this monograph, it is important to note that oral ALA also has many indications and a larger body of research, comparatively. Many of the existing studies in people with cancer using IV ALA also combine it with oral ALA post-IV administration.[38,39]

Adverse Events and Side Effects

With IV administration, local pain during infusion and redness are common. Of the few studies using IV administration for cancer, significant adverse effects have not been reported.[21,38-40] High doses of 300-600 mg/day IV ALA for 2-4 weeks have been studied in a few clinical trials and were considered safe.[39,44,46] A case series (N = 11) previously described, used IV ALA at 600 mg/day as part of a larger metabolic treatment, and reported that none of the patients experienced significant side effects.[40] Another single-arm study (N = 14) using IV ALA, followed by a period of oral ALA at 1800 mg taken three times a day for taxane-induced neuropathy reported only moderate gastric pain (2/14 patients) and grade 1 and 2 nausea in one patient each.[39]

In a systematic review and meta-analysis of fifteen RCTs assessing ALA for diabetic peripheral neuropathy, treatment with 300-600 mg IV ALA daily resulted in no serious adverse effects.[44] The most common side effects reported was stomach upset (three patients). In another systematic review, doses greater than 600 mg/day resulted in a higher incidence of nausea, vomiting and dizziness.[46] More research from well controlled studies in cancer populations is needed to assess safety in the context of cancer care.

Interactions with cancer treatments and other medications

Chemotherapy and radiation therapy:

Human studies have used ALA with chemotherapy (docetaxel, cisplatin, oxaliplatin and gemcitabine), however none report on long-term outcomes.[38,39,47,48] However, due to ALA's antioxidant properties, including regenerating glutathione,[20,21,49] it may negatively interfere with the effectiveness of radiation and chemotherapy.[50,51] Indeed, preclinical research has identified ALA as a radioprotective agent.[52] Until more research is available evaluating clinical outcomes with combined use, ALA

should be used cautiously alongside chemotherapy and radiation therapy.

Other medications:
ALA may interfere with thyroid metabolism and it can interfere with the production of T3 from T4 when it is co-administered with T4.[53]

There is a theoretical risk of hypoglycemia when using oral hypoglycemic agents along with ALA due to the supportive effect of ALA on glucose and insulin metabolism. Diabetic patients taking ALA should closely monitor their blood glucose levels particularly if just starting with ALA and if insulin management is required.

Due to the limited research available on combining conventional treatments with ALA, each case requires evaluation to determine the overall risks and benefits of proceeding with treatment.

Cautions and Contraindications

Due to the risk of oral ALA potentiating hypoglycemia in diabetic patients, and animal reports of IV ALA inducing hypoglycemia in fasting nondiabetic and diabetic rats,[54] ALA should be administered with caution in patients with diabetes or other endocrine disorders that may have an impact on glycemic regulation.

There is not enough research on the use of IV ALA in pregnancy or lactation to comment on safety. There is some data to support the use of oral ALA in high-risk pregnancies. A 2021 review describes four RCTs and one observational study on the beneficial use of oral ALA and vaginal capsules in high-risk pregnancies.[55]

ALA should be used cautiously in those with a thiamine deficiency or risk of thiamine deficiency (e.g. alcoholics, those with malnutrition) based on animal studies. In these patients, supplementation with thiamine is recommended. In animal studies using ALA, doses greater than 20 mg/kg administered intraperitoneally proved to be fatal in severely thiamine-deficient rats: an effect that was prevented when ALA was administered simultaneously with thiamine hydrochloride.[56]

Dosing, frequency and length of treatment

IV doses of ALA are most commonly prescribed in the 300-600 mg range, 1-2 times per week, for 3-5 weeks in single-arm trials, and >12 months in some case reports.[38-40,46]

The maximum tolerated dose has not yet been established, but there are reports of overdose of oral ALA with doses of 4.5g and 6g causing death and multiorgan failure.[57,58]

Disclaimer

This monograph provides a summary of available evidence and neither advocates for nor against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.

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